REMARKS

The specification has been amended to clarify the title of the application, and to correct errors identified in the Office Action.

Claims 2-12 remain pending in the application. The limitations of original independent claim 1 have been merged into claim 2, and claim 1 has been canceled. Original claim 13 has also been canceled. Errors in claim numbering have been corrected, resulting in previous claim 11 being renumbered as claim 10, and previous original claim 12 (first occurrence) being renumbered as claim 11. Other claim amendments have been made to correct typographical errors and improve claim readability.

None of the amendments results in an addition of new matter, and their entry is appropriate at this time. Cancellation of any subject matter of the original claims is not be construed as an abandonment of such subject matter, as the Applicants specifically reserve the right to again present the subject matter in this or a continuing application.

The claims were rejected, and the specification and claims objected to, on various grounds, and these will be discussed separately below.

Objection to the Specification

Informalities were described in the Office Action at locations on pages 12, 22, and 23 of the specification. Each of these has been corrected by the present amendment, so the objections should be withdrawn.

Objection to the Claims

An objection in the Office Action related to an error in the numbering of claims 11 and 12 (first occurrence). Applicants note that there was no claim numbered 10. The numbering has been corrected by this amendment, so the objection should now be withdrawn.

The spelling error identified in claims 6 and 7 has been corrected, and the incorrect indicia for subparagraphs in claims 4 and 5 have been removed, so those objections should also now be withdrawn.

First Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, and 13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 4,713,246 to Begum et al, in view of U.S. Patent 5,993,858 to Crison et al. Of these rejected claims, only claim 2 is presently pending.

Begum et al. described oral pharmaceutical dosage forms containing the drug etoposide, which dosage forms are gelatin capsules containing the drug dissolved in a mixture of propylene glycol, a bile acid, a water-soluble acid, ethanol, and water. The composition is said to form a "micellar solution" of etoposide upon contact of the capsule contents with stomach fluid. It was stated that micellar solubilization of other drugs having low water solubility is mediated by bile acids, as was reported in the scientific literature.

Crison et al. described a self-emulsifying formulation for increasing the solubility of a drug. The formulation contains an oil, a surfactant, and a hydrophilic co-surfactant having a HLB value greater than 8. Formulations of nifedipine prepared with a hydrophilic co-surfactant had twice the bioavailability in dogs of the bioavailability obtained with a formulation prepared using a lipophilic co-surfactant.

Applicants respectfully submit that no meaningful combination can be made from the teachings of these cited documents. The critical component of the Begum et al. patent is a bile acid, and no mention of that component appears in the Crison et al. patent. The critical component of the Crison et al. patent appears to be the hydrophilic co-solvent, and Begum et al. do not include a discussion of discuss surfactants. Begum et al. discuss only use of the drug etoposide, while Crison et al. describe nifedipine and a few other drugs, not chemically related to etoposide. Those skilled in the pharmaceutical formulation art are aware that different drugs behave differently in combinations with different formulation excipients, and that interchangeability of drugs in specific formulations is quite rare.

Moreover, there is no direction toward making a combination of teachings from the two documents that meets the limitations of Applicants' claim 2, that claim requiring the combination of: a drug phase comprising etoposide and a solvent; a co-solvent; and an emulsifying base comprising a lipid, a surfactant and a stabilizer; in a capsule shell.

Without such direction, a large number of experiments would have to be performed with various permutations of the formulation components disclosed in the documents, to see if any useful etoposide formulation results. There can be no reasonable expectation at the outset that such experimentation would be successful.

As set forth in M.P.E.P. § 2143, there must be some suggestion or motivation to modify a reference or to combine reference teachings, or no *prima facie* case for obviousness will be established. The section also states a requirement that the teaching or suggestion, and a reasonable expectation of success, must both be found in the prior art, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). A further discussion of the principle, and additional case law support, is found in M.P.E.P. § 2143.01. There is no such teaching or suggestion in the presently cited documents, indicating that the rejection does not comply with applicable law.

The cited patents cannot establish obviousness of claim 2 under current legal standards, and this rejection should therefore be withdrawn.

Second Rejection Under 35 U.S.C. §103(a)

Claims 3-12 (presumed to correspond with claims so numbered, after entry of this amendment) were rejected under 35 U.S.C. § 103(a) as being unpatentable over the above-discussed combination of the Begum et al. and Crison et al. patents, further in combination with U.S. Patents 4,772,589 to Kaplan et al. and 5,342,625 to Hauer et al. Kaplan et al. teach solutions comprising etoposide, 1-methyl-2-pyrrolidone and an acid, that can be diluted with common infusion media without drug crystallization or filled into capsules. Hauer et al. teach cyclosporin microemulsion compositions for topical application and compositions for oral administration.

Neither of the Kaplan et al. nor Hauer et al. patents, nor the patents taken together, overcomes the deficiencies of the Begum et al./Crison et al. combination discussed above for establishing obviousness. Kaplan et al. do not discuss a need for any surfactants, co-solvents, or anything else in their formulations, and therefore making combinations that include such other substances would not be a logical extension of the teachings. Hauer et al. do not disclose anything relating to etoposide

or other drug compounds that are not cyclosporins, and no information is in the record to establish a chemical similarity between these drug compounds.

The decisional law is clear that one cannot pick and choose isolated teachings from various cited documents, and then combine the teachings to make a case for obviousness. *In re Fine*, 837 F.2d 1071 (Fed. cir. 1988) states: "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." This principle goes hand-in-hand with the above-discussed principle that a suggestion or motivation must be present in the art, to justify a combination of reference teachings in making an obviousness rejection.

The Kaplan et al. patent teaches that a dosage form can be made simply by placing a solution of etoposide and an acid in 1-methyl-2-pyrrolidone, into soft gelatin capsules. It does not pertain in any manner to self-microemulsifying compositions, and does not suggest that any other ingredients need to be added to its disclosed compositions, or any benefit would thereby be obtained.

There is no reason for one having ordinary skill in the art to consult the Hauer et al. patent, pertaining solely to cyclosporin compositions, for guidance regarding formulating etoposide compositions, as the two drugs have not been shown to be chemically or therapeutically similar.

Whether or not all of the claim-recited ingredients are known in the art is not particularly relevant to the question of obviousness, absent some suggestion or motivation to assemble the specific combinations required by the claims.

In view of these deficiencies, the rejection of claims 3-12 for obviousness is not legally proper and should not be maintained, upon reconsideration.

CONCLUSION

As discussed above, the objections to the specification and claims have been overcome and the rejections were not in compliance with applicable legal requirements. Accordingly, it appears that all of the pending claims 2-12 are patentable and a notice of their allowability is respectfully solicited.

If there are any matters remaining to be resolved before disposition of the application, and resolution might be obtained by means of a telephonic or personal interview, please contact the undersigned using the information given below to arrange the interview.

Respectfully submitted,

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